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Bladder Cancer Risk and Pipes, Cigars, and Smokeless Tobacco

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Interview data from 2982 patients with bladder cancer and 5782 controls selected from the general population were used to assess the effects of non-cigarette tobacco use on bladder cancer risk. Compared to men who had never smoked, those who had smoked pipes but not cigars or cigarettes had a relative risk estimated at 1.23 (95% confidence interval [CI] = 0.75–2.00). Those who smoked cigars but not pipes or cigarettes were estimated to have a relative risk of 1.33 (95% CI = 0.92–1.94). Little evidence of dose response was observed. The excess relative risk to pipe smokers was limited to those who inhaled deeply.

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THERE IS PERSUASIVE EVIDENCE that cigarette smoking can cause human bladder cancer, but whether pipe smoking, cigar smoking, snuff dipping, or tobacco chewing can do so remains unclear. In some epidemiologic studies, pipe smoking has been associated with bladder cancer,[1–6] whereas in other studies it has not.[7,8] Cigar smoking has been associated with bladder cancer in some[1,5,7] but not other[3,6,8] studies. Snuff users have been estimated to have relative risks (RR) near[7] or below[2] the null value, and tobacco chewers have been estimated to have RR near[5,7] or above[2] the null value. Epidemiologic study of bladder cancer and non-cigarette tobacco has been hampered by the relatively small number of people who have used these tobaccos but have not smoked cigarettes.

Because many of the carcinogenic compounds that appear in cigarette smoke also appear in other tobacco products, a link between these products and bladder cancer is plausible. We therefore estimated the effects of non-cigarette tobacco exposures on bladder cancer risk using data obtained from interviews conducted for a large case–control study of bladder cancer.

Methods

We interviewed 2982 cases and 5782 controls as part of the National Bladder Cancer Study, a collaborative population-based case–control study conducted in ten geographic areas of the US.[9] The case group was composed of all identified residents of the areas aged 21 to 84 who were diagnosed with histologically confirmed bladder cancer in a 1-year period (with the beginning time varying among areas from December 1977 to March 1978).

Cases were identified from cancer registries, nine of which were part of the National Cancer Institute (NCI) Surveillance Epidemiology and End Results (SEER) Program. The control group was randomly selected from the general population (weighted by the age, sex, and geographic distribution of the cases). Controls ages 21 to 64 were selected from 22,633 households chosen by telephone sampling using random-digit dialing. Controls aged 65 to 84 were selected from Health Care Financing Administration rosters. Details of the study methods are presented elsewhere.[10]

We identified 4086 eligible cases and interviewed 2982 (73%) of them. The remaining 1104 were not interviewed because of death (282), illness (288), patient refusal (252), physician refusal (128), being identified after the study ended (65), not being found (81), and other reasons (8). A total of 4057 older controls were eligible, of whom 3313 (82%) were interviewed. The

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TABLE 1. Patterns of Non-Cigarette Tobacco Use, Among Male Population Controls

Subgroups	Total	Percent ever used			
		Pipes	Cigars	Snuff	Chewing tobacco
All men	4282	33	26	5	12
Race					
White	3892	33	26	5	11
Nonwhite	390	26	27	5	18
Age					
21–44	240	15	13	0	2
45–64	1653	30	21	3	6
65–84	2389	36	31	7	16
Smoking history					
Never smoked cigarettes*	1285	22	27	4	10
Former smoker	1642	40	32	6	13
Current smoker	1101	30	16	5	12
Area of residence					
Atlanta	186	36	25	8	23
Connecticut	654	37	31	4	12
Detroit	355	33	36	8	20
Iowa	552	41	24	12	14
New Jersey	1288	29	26	2	10
New Mexico	129	29	21	7	20
New Orleans	115	19	22	1	6
San Francisco	542	34	26	2	8
Seattle	255	34	22	10	6
Utah	206	20	12	5	7
Job exposure†					
Yes	1430	33	26	6	13
No	2852	33	26	5	11

* Excludes 252 smokers with unknown dates and 2 subjects with unknown smoking history.

† To dyes, rubber, leather, inks, or paints.

remaining 744 were not interviewed because of death (94), illness (174), refusal (348), not being found (105), and other reasons (23). From telephone sampling of households, 2928 people younger than 65 were selected as controls, of whom 2469 (84%) were interviewed. The remaining 459 were not interviewed because of death (7), illness (23), refusals (335), not being found (87), and other reasons (7).

All subjects were interviewed at home. Interviewers used a questionnaire that included questions about the use of artificial sweeteners, hair dyes, and tobacco products, and about occupational and residential history. Respondents were asked whether they had ever used pipes, cigars, chewing tobacco, or snuff for 6 months or more, prior to 1 year before interview (that is, before onset of the cases' illness). They were asked how much they had used each week and how many years they had used it. For cigars and pipes, they were also asked how deeply they had inhaled. For snuff, they were also asked whether they had used it by nose or mouth.

The effect of tobacco use on bladder cancer risk was estimated by the observed RR. Maximum likelihood estimates were derived from multiple logistic regression models with terms entered for the exposures and for potentially confounding variables. The estimates given were adjusted for race (white, other), age (21–44, 45–64, 65–84), and residence (in four groups). Finer adjustment for age or residence did not alter the estimates.

Approximately 75% of the interviewed cases (and controls) were men. Among the women in the study, only 9 had smoked pipes, 7 had smoked cigars, 21 had used snuff, and 14 had chewed tobacco, so analysis was restricted to male cases and controls.

Results

In total, 41% of the male controls interviewed were former cigarette smokers and 27% were current cigarette smokers. As Table 1 shows, 33% of male controls had smoked pipes at some time, 26% had smoked cigars, 5% had used snuff, and 12% had chewed tobacco. A history of pipe smoking was more common among white men, older men, and former cigarette smokers. Cigar smoking was more common among older men and former smokers. It was least common among current cigarette smokers. Pipe and cigar smoking were most prevalent in Iowa and Detroit and least prevalent in Utah. Snuff use was more prevalent in Iowa and Seattle than elsewhere, and chewing tobacco use was most

TABLE 2. Estimated Relative Risk of Bladder Cancer, Among Men, According to Whether Smoking Currently, Age Started, and Average Daily Smoking Frequency

	Age started	Average daily frequency	Cases	Controls	Estimated RR*	95% CI
Not currently smoking	20	<20	70	229	1.1	0.8–1.5
		20–39	109	238	1.6	1.3–2.1
		40	54	116	1.7	1.2–2.4
	15–19	<20	101	224	1.6	1.2–2.1
		20–39	212	338	2.2	1.8–2.8
		40	90	173	1.9	1.4–2.5
	<15	<20	29	75	1.4	0.9–2.2
		20–39	78	153	1.8	1.4–2.5
		40	61	77	2.8	2.0–4.0
Currently smoking	20	<20	59	129	1.7	1.2–2.4
		20–39	125	176	2.7	2.0–3.5
		40	31	45	2.5	1.5–4.0
	15–19	<20	87	139	2.4	1.8–3.2
		20–39	275	290	3.5	2.9–4.3
		40	70	65	4.0	2.8–5.8
	<15	<20	39	48	3.2	2.1–5.0
		20–39	146	152	3.6	2.7–4.6
		40	61	52	4.3	2.9–6.4

* Relative to 352 cases and 1285 controls who never smoked, adjusted for age, race, and geographic area.

RR: relative risk; CI: confidence interval.

prevalent in Atlanta, Detroit, and New Mexico. A history of occupational exposure to dyes, rubber, leather, inks, or paints was unrelated to tobacco use.

Table 2 shows the rate ratios for bladder cancer, estimated according to various measures of exposure to cigarette tobacco. Men who had ever smoked cigarettes showed an estimated RR of 2.2 (95% confidence interval [CI] = 2.0–2.6). Early age at starting, heavy smoking, and current smoking increased the estimated risk.

Compared to men who had never smoked pipes or cigars, those who smoked pipes but not cigars had an estimated RR of 0.96 (95% CI = 0.82–1.12), adjusted for the measures of cigarette smoking shown in Table 2. The corresponding estimate for cigar smoking was 0.97 (95% CI = 0.80–1.18), and for both pipes and cigars it was 0.94 (95% CI = 0.80–1.11). The unadjusted estimates were lower than these adjusted estimates; that is, they were negatively confounded by cigarette smoking. Because of the likelihood of residual, uncontrolled confounding, we examined the group of men who had never smoked cigarettes. Table 3 presents the estimated RR within this group. The men who smoked pipes, cigars, or both had slightly higher relative risks than the men who had used no tobacco (1.23, 1.33, and 1.40, respectively). The small number of snuff users yielded a relatively unstable estimated RR of 0.77 (95% CI = 0.38–1.56). The 173 users of chewing tobacco showed no excess RR (RR = 1.02; 95% CI = 0.67–1.54).

TABLE 3. Estimated Relative Risk of Bladder Cancer, Among Men Who Never Smoked Cigarettes, According to History of Use of Other Tobaccos

	Cases		Controls		Estimated RR*	95% CI
	No.	Percent	No.	Percent		
None	196	56	799	62	1.00	
Pipes but not cigars†	24	7	80	6	1.23	0.75–2.00
Cigars but not pipes†	48	14	142	11	1.33	0.92–1.94
Pipes and cigars†	72	21	206	16	1.40	1.01–1.93
Snuff‡	11	3	50	4	0.77	0.38–1.56
Chewing tobacco§	40	11	133	10	1.02	0.67–1.54

* Adjusted for race, age, and residence.
† Also adjusted for snuff and chewing tobacco.
‡ Also adjusted for pipes, cigars, and chewing tobacco.
§ Also adjusted for pipes, cigars, and snuff.
RR: relative risk; CI: confidence interval.

TABLE 4. Estimated Relative Risk of Bladder Cancer, According to Pipe-Smoking History, Among Men Who Never Smoked Cigarettes

	Cases		Controls			
	No.	Percent	No.	Percent	RR*	95% CI
Never smoked pipes	255	72	996	78	1.00	
Pipe smokers						
Inhalation						
Not at all	78	22	235	18	1.08	0.76–1.52
Mouth or throat	9	3	38	2	0.81	0.37–1.74
Chest	10	3	12	1	3.14	1.32–7.47
Duration (yr)†						
<20	46	13	134	10	1.18	0.78–1.79
20–39	20	6	71	6	0.94	0.54–1.66
40–59	21	6	57	4	1.18	0.69–2.02
60	9	3	19	1	1.45	0.63–3.33
Average weekly pipefuls smoked						
<14	32	9	85	7	1.25	0.78–1.99
14–27	23	7	81	6	0.93	0.55–1.57
28–41	14	4	40	3	1.11	0.58–2.13
42	18	5	63	5	0.94	0.54–1.66
Lifetime dose (pipe-yr)‡						
<20	29	8	95	8	1.03	0.64–1.65
20–39	11	3	37	3	1.02	0.49–2.11
40–99	18	5	39	3	1.49	0.81–2.74
100	28	8	94	7	0.97	0.61–1.56

* Adjusted for race, age, and residence, and whether subject ever smoked cigars.
† Additionally adjusted for age in decades.
‡ One pipe-yr equals 365 pipefuls.
RR: relative risk; CI: confidence interval.

Table 4 is also limited to men who had never smoked cigarettes. It shows that the observed excess RR of the pipe smokers was restricted to those who inhaled the smoke into their chests. Among the 22 deep inhalers, both duration and intensity of pipe smoking were consistently related to risk. The estimated RR among all

TABLE 5. Estimated Relative Risk of Bladder Cancer, According to Cigar-Smoking History, Among Men Who Never Smoked Cigarettes

	Cases		Controls			
	No.	Percent	No.	Percent	Estimated RR*	95% CI
Never smoked cigars	232	66	934	73	1.00	
Cigar smokers						
Inhalation						
Not at all	99	28	290	23	1.23	0.66–2.30
Mouth or throat	16	5	41	3	1.41	0.19–2.63
Chest	4	1	16	1	1.09	0.36–3.33
Duration (yr)†						
<20	46	13	139	11	1.24	0.83–1.86
20–39	30	9	103	8	1.03	0.64–1.65
40–59	34	10	89	7	1.38	0.87–2.17
60	8	3	15	1	1.72	0.69–4.31
Average weekly cigars smoked						
<14	56	16	168	13	1.22	0.83–1.80
14–27	32	9	87	7	1.33	0.83–2.11
28–41	16	5	42	3	1.41	0.76–2.61
42	15	4	51	4	1.04	0.56–1.92
Lifetime dose (cigar-yr)‡						
<20	41	12	138	11	1.12	0.74–1.71
20–39	19	5	38	3	1.91	1.03–3.52
40–99	22	6	75	6	1.03	0.61–1.76
100	35	10	94	7	1.32	0.85–2.06

* Adjusted for race, age, and residence, and whether subject ever smoked pipes.
† Additionally adjusted for age in decades.
‡ One cigar-yr equals 365 cigars.
RR: relative risk; CI: confidence interval.

TABLE 6. Other Studies of Bladder Cancer, and Pipes and Cigars

Study	Population	Smoking history		
		Pipes	Cigars	Both
Lockwood;[1]	369 prevalent cases, Denmark 369 neighborhood controls	1.6* (0.9–2.8)	2.0 (1.0–3.7)	
Wynder *et al.*[2]†	300 prevalent cases, New York 300 hospital controls	2.2 (0.7–7.4)	0.8 (0.3–2.1)	1.3 (0.5–3.3)
Kahn[3]*†	293,000 US veterans followed 8.5 yr	1.2 current 0.5 former	0.9 current 1.1 former	1.2 current 2.4 former
Cole[7]	360 incident cases, Boston 381 population controls	1.1	1.2	
Wynder *et al.*[8]†	574 prevalent cases, US 574 hospital controls	0.7 (0.3–1.9)	0.9 (0.5–1.7)	1.0 (0.5–2.3)
Williams *et al.*[4]	206 incident cases, US 2683 cancer controls	1.4 moderate 1.6 heavy	1.4 moderate 1.0 heavy	
Howe *et al.*[5]	480 incident cases, US 480 neighborhood controls	1.3 moderate (0.7–2.2) 2.0 heavy (1.2–3.5)	1.2 (0.7–2.0)	
Morrison *et al.*[6]†	592 incident cases, Boston 543 population controls 553 incident cases, UK 731 population controls	1.7 (0.8–3.6) 3.9 (1.3–11.8)	1.0 (approx) 1.0 (approx)	

* Estimated relative risk (95% confidence interval).

† Estimates among men who had never smoked cigarettes.

pipe smokers did not parallel reported usual dose-rate or estimated lifetime dose. Men who had smoked pipes for 60 years or longer showed higher RR than those who had smoked for fewer years, but the relation between duration and estimated RR was not statistically significant ($P = 0.41$). Among men aged 65 or older, the duration-specific estimates corresponding to those in Table 4 were 1.15, 1.05, 1.36, and 1.46, respectively. Among men younger than 65, there was an inverse association between duration and estimated RR.

As Table 5 shows, there was no clear relation between estimated RR and intensity, total dose, or depth of inhalation of cigars. Duration of cigar smoking was weakly related to risk, but not significantly so ($P = 0.15$).

The 25 men who had smoked more than 28 cigars weekly and more than 28 pipefuls of tobacco weekly did not show an elevated RR. The 38 men who had smoked pipes for more than 40 years and cigars for more than 40 years did show an elevated RR (RR = 1.92, 95% CI = 0.94–3.89).

Discussion

Tobaccos contain thousands of compounds, including many known or suspect carcinogens.[11] Although non-cigarette tobaccos have not been as extensively studied as cigarette tobaccos, the former contain many of the same compounds as the latter, including some likely to be human carcinogens. For example, cigar smoke contains more 3,4-benzpyrene, pyrene, and anthracene than does cigarette smoke.[12] Pipe smoke contains as much as or more of several polycyclic aromatic hydrocarbons as does cigarette smoke. Noncombustible tobaccos contain more nitrosamines than either cigars or cigarettes do.[13] It is therefore not surprising that these non-cigarette tobaccos have been linked to various malignancies. Whether human bladder cancers can be induced by these tobaccos depends not only on their chemical composition but also on the ways they are used and on the unknown details of the passage from the mouth, nose, or lungs to the urinary bladder.

Our findings suggest that pipe smokers and possibly cigar smokers face a 20% to 40% higher risk of bladder cancer than do nonsmokers, but not as high a risk as cigarette smokers. On the other hand, our data show no evidence of dose response and therefore warrant cautious interpretation. Our data suggest that snuff users and tobacco chewers are not at increased risk.

The observed increased risk in pipe smokers who inhaled deeply is plausible and has been reported elsewhere.[5] The apparent lack of an effect of cigar inhalation is puzzling. We did not have the information to assess

possible effects of latent period or age at exposure. The absence of an observed dose–response relation for duration, intensity, or total dose of exposure to either pipes or cigars is also peculiar, if cigars and pipe tobacco can cause bladder cancer. It is possible that misclassification of the dose data obscured a real effect. Alternatively, the small overall increase in risk seen for cigar or pipe smokers (20%–40%) could have been artifactual. (For example, if cigar or pipe smokers included men who formerly smoked cigarettes but claimed not to have smoked, the measured effect of pipes and cigars would be inflated.)

Our observation that snuff dippers and tobacco chewers were not at increased risk of bladder cancer is consistent with the few published data[2,5,7] but all of the existing estimates are too unstable to permit any firm conclusions to be drawn.

Our findings on pipe smoking and cigar smoking are generally consistent with other published data, summarized in Table 6. The estimates presented in Table 6 are not strictly comparable to each other or to ours because of differences in study design, outcome measures (incidence, prevalence, or mortality), the inclusion of former or current cigarette smokers, or adjustments made in the analysis. The studies most similar to the current investigation[5–7] yielded similar findings. One strength of the current study is the large number of subjects, permitting more precise estimates in an analysis restricted to men who did not smoke cigarettes.

In sum, cigarette smokers have twice the risk of bladder cancer that nonsmokers have, but users of noncigarette tobaccos have only slightly elevated (20%–40%) risks. Whether typical cigar or pipe smoking has caused bladder cancer remains unclear. Pipe smokers who inhale deeply appear to have measurably elevated bladder cancer risks.

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